Remarks

Rejections under 35 U.S.C. § 103

Claims 1-3, 5-8, 19, 20, 22-24, and 27-32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Holmes et al. (5,955,343), hereinafter "Holmes" in view of Hubbell (6,129,761), hereinafter "Hubbell". Applicants respectfully traverse this rejection for each of the reasons set forth below. As set forth in more detail below, Applicants maintain that (i) The Examiner has used hindsight in asserting that Holmes suggests the claimed invention when if anything he teaches away from it; (ii) The combination of Holmes and Hubbell fails to enable the invention because neither of them teaches or suggests the use of a solute that does not induce peptide self-assembly but provides sufficient osmolarity to maintain cell viability. The Examiner has failed to address Applicants' arguments raised in the office action response filed June 2, 2004, regarding the importance of using such a solute in order to meaningfully enable the claims; and (iii) The Examiner has failed to give due weight to the secondary considerations described in the previous office action response.

Firstly, Applicants submit that the Examiner uses hindsight to draw unwarranted conclusions from certain statements of Holmes and overlooks certain elements of the instant claims in the rejection. The Examiner correctly indicates that, "Holmes et al disclose culturing cells on a membrane or matrix formed by self-assembling peptides". The Examiner then asserts that, "The structures produced can also encapsulate cells..." and refers to col. 12, lines 4-9. However, Applicants submit that one of ordinary skill in the art, reading col. 12, lines 4-9, in the context of the immediately preceding sentences in the paragraph, would not conclude that Holmes describes or suggests the encapsulation of cells in a macroscopic scaffold *formed by the peptides self-assembling to encapsulate living cells* as recited in the instant claims. Holmes states, "Many cells require adherence to a surface, such as tissue culture plastic, resulting in a surface-to-volume limitation. The biopolymer materials of the present invention, containing cells, can be stacked in a vessel containing culture medium, improving the density of cells grown in this manner. The porous microstructure of the biopolymers can also be useful for encapsulating cells. The pore size of the membrane is large enough to allow the diffusion of cell products and nutrients..." The word "encapsulate" has been defined as "to encase as in a

capsule", while "encapsulated" has been defined as, "enclosed by a protective coating or membrane, as in certain bacteria" (American Heritage Dictionary, Second College Edition, 1985). Applicants submit that one of ordinary skill in the art considering the above passage in the context of the remainder of Holmes, which refers extensively to membranes and culturing cells thereon, would not envision encapsulating cells by inducing peptide self-assembly in the presence of cells but would more likely envision enclosing cells by forming a stack of membranes having cells attached thereto, or perhaps embedding cells in a structure formed from the peptides after their self-assembly.

The very fact that Holmes repeatedly refers to his structures as membranes and repeatedly describes culturing cells *on* the membranes after their formation, would tend to lead one of ordinary skill in the art away from the notion of attempting to encapsulate cells using methods similar to those of Hubbell. Thus neither Holmes nor Hubbell, nor the combination thereof, renders the claimed invention obvious.

Secondly, as discussed during the phone interview and described at length in the previous office action response filed June 2, 2004, the methods taught by Holmes and Hubbell fail to enable the instant claims. The skilled artisan reading Holmes and Hubbell would not be led to a workable method of producing the claimed macroscopic scaffold encapsulating living cells.

Holmes discloses a method in which peptides are added to tissue culture medium of cultured cells, which resulted in the formation of membranes that did not encapsulate the cells (see, e.g., col. 3, lines 32-35 of Holmes). Holmes further discloses that various monovalent cations can induce membrane formation (see, e.g., col. 7, lines 50-60). Holmes does not discuss how these teachings might be modified to encapsulate living cells by peptide self-assembly. Hubbell describes dissolving a polymer in an aqueous solution, preferably a 0.1 M potassium phosphate solution, at physiological pH, to a concentration forming a polymeric hydrogel and suspending isolated cells in the solution (col. 10, lines 31-33). However, if the skilled artisan were to adopt a similar approach using the peptides of the present invention rather than the polymers taught by Hubbell, the result would be almost instantaneous self-assembly of the peptides after their addition to the aqueous solution as a result of the presence of the electrolyte (phosphate). Thus it would not be possible to add the cells and achieve a three-dimensional arrangement of cells within the resulting gel. The Examiner indicates that the skilled artisan

reading Holmes would be aware of this difficulty and would therefore combine cells with peptides without salt and only then add salt. However, as discussed during the phone interview on Feb. 15, 2005, the inventors discovered that without further modifications not suggested by Holmes or Hubbell, *this method will not work to produce a macroscopic scaffold that is useful for purposes such as those described in the instant application or in Hubbell.* If the cells are maintained in tissue culture medium prior to being combined with peptides, self-assembly will immediately begin upon combining the medium containing the cells with the peptide solution. Attempts to distribute the cells within the scaffold as it forms will fracture the scaffold and will not result in a three-dimensional arrangement of cells as recited in the instant claims. The result will be an inhomogeneous mixture of small chunks of gel, not useful as a macroscopic scaffold. The alternative is to suspend the cells in an aqueous solution that lacks electrolytes found in tissue culture medium (e.g., pure water), add the cells to the peptide solution, and then add salt. However, *this approach results in lysis of the cells* in a time frame so rapid that it is not possible to effectively distribute cells to achieve a three-dimensional arrangement of living cells, pour the mixture into a mold, or inject it into a subject, as would typically be done with a macroscopic scaffold in the real world.

In order to avoid lysis of the cells during the time reasonably needed to mix and distribute the cells and perform additional maneuvers such as pouring or injecting the material, the cells must be maintained in a medium having sufficient solute concentration such that that is substantially iso-osmotic with respect to the interior of the cells, i.e., the concentration of osmotically active agents (e.g., monovalent cations, carbohydrates, etc.) inside and outside the cells must be substantially similar. If the concentration outside the cells is too low, water will rapidly move into the cells and they will burst. The inventors, recognizing this fact, developed methods for avoiding it. For example, a preferred method of producing a scaffold encapsulating cells "involves incubating peptides and living cells in an aqueous solution having an iso-osmotic solute, preferably under conditions that do not allow the peptides to substantially self-assemble." This step is followed by addition of an electrolyte, which allows self-assembly to proceed. (See p. 2, lines 18-21). See also p. 15, lines 1-5, stating, "We have discovered that a peptide scaffold that encapsulates living cells in a three-dimensional arrangement may be formed by first mixing the cells and the peptides in a solution having the required osmolarity to maintain cell viability,

and then adding sufficient electrolytes to initiate self-assembly of the scaffold." For example, the scaffold encapsulating cells may be formed by dissolving peptides in an iso-osmotic solution in the absence of electrolyte, resuspending cells in the solution, introducing the solution into a casting frame or mold, and then exposing the solution to a sufficient concentration of electrolyte to allow self-assembly to occur (p. 23, line 24 – p. 24, line 6). Applicants describe in detail the use of sucrose as an osmotically active solute at p. 23, lines 23-24 to facilitate production of a macroscopic scaffold encapsulating living cells.

In summary, a macroscopic scaffold encapsulating cells formed according to the methods described in the instant application differs materially from a structure that might be formed by following methods taught by Holmes or Hubbell or modifications that would be obvious to one of ordinary skill in the art based on reading these references. Applicants further note that it was not obvious that self-assembly would proceed even in the presence of an iso-osmotic solute, i.e., that the presence of substantial concentrations of a molecule such as sucrose would not interfere with gel formation. As the Federal Circuit has repeatedly affirmed, " 'In order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method.' " *Motorola, Inc. v. Interdigital Technology Corp.*, 121 F.3d 1461 (Fed. Cir. 1997), quoting from *Beckman Instruments, Inc. v. LKB Produktur AB*, 892 F.2d 1547 (Fed. Cir. 1989). Even if the teachings of Hubbell could be said to suggest the use of self-assembling peptides to form hydrogels encapsulating viable cells, neither Holmes, Hubbell, or a combination of both discloses how to actually achieve this result. In particular, these references do not suggest the importance of maintaining the cells and peptides in the presence of a sufficient amount of an osmotically active agent prior to exposure to the electrolyte.

In the previous office action response Applicants pointed out a number of secondary considerations that support a determination of non-obviousness. Applicants drew the attention of the Examiner to the fact that Holmes disclosed self-assembling peptides and membranes formed therefrom in *Proceedings of the National Academy of Sciences* (*PNAS*) in April 1993, and Hubbell failed to mention such peptides as possible materials to use for encapsulating cells in his patent application filed June 7, 1995, suggesting that he did not consider them suitable or that the idea was not obvious to him. The Examiner responded that Hubbell may not have known of the

Holmes paper. Applicants submit that it is highly unlikely that Hubbell was not aware of the Holmes paper given that *PNAS* is an extremely prominent and widely read journal and that Hubbell was at least a person of ordinary skill in the field of tissue engineering materials in 1995 at the time of filing his patent application, as conceded by the Examiner. Applicants submit that Hubbell, who is Professor and Director of the Institute for Biological Engineering and Biotechnology at the Ecole Polytechnique Fédérale (Swiss Federal Institute of Technology) in Lausanne, Switzerland (see Exhibit D submitted with previous office action response) was and is in fact an expert in the field. If, as the Examiner contends, a person of ordinary skill in the art would be aware of Holmes and Hubbell and would have found the instantly claimed invention obvious, then surely Hubbell himself as a person of more than ordinary skill in the art would be aware of the 1993 Holmes paper and would have suggested that the self-assembling peptides could be used similarly to the polymers suggested in his patent.

Furthermore, Hubbell's PCT application WO9640304, virtually identical to his U.S. patent, was published in December 1996, but the first full publication reporting successful encapsulation of living cells in the self-assembling peptides was a Research Report in the *Proceedings of the National Academy of Sciences* in 2000. This lengthy gap strongly suggests that the invention was by no means obvious. The Examiner has asserted that publication in a scientific journal does not establish that the invention is unobvious. Applicants draw the attention of the Examiner to Exhibit A, which is a copy of the *PNAS* Information for Authors and notes that *PNAS* Research Reports "describe the results of original research of exceptional importance". Applicants further draw the Examiner's attention to Exhibit B, which provides information about *PNAS* and indicates that it is one of the world's most-cited multidisciplinary scientific serials and publishes "cutting edge research reports". Applicants submit that given this evidence of the standards *PNAS* maintains for publication it is highly unlikely that a report describing the claimed invention would have merited publication by the journal if it was obvious based on previous work.

Applicants further presented a review article authored by Jeffrey A. Hubbell (i.e., the inventor of the Hubbell patent), which refers to the inventors' paper in the *Proceedings of the National Academy of Sciences* (2000) as "of outstanding interest". The Examiner inappropriately discounts this evidence of nonobviousness. The Examiner firstly says that the

Hubbell article cannot render the invention nonobvious at the time the application was filed since the article was published after the application was filed. Applicants respectfully disagree. Clearly if the invention was nonobvious in 2003, when the Hubbell article was published, it would have been nonobvious in 2001, when the application was filed. It is highly unlikely that the invention would have been obvious in 2001 and have become less so during the intervening time period.

The Examiner further asserts that "Hubbell makes no statement with regard to being obvious or nonobvious." Applicants submit that it is hardly likely that Hubbell would see fit to comment explicitly on the obviousness or nonobviousness of a paper he discusses. Such commentary is virtually never found in a review article as it is superfluous, given the fact that the referenced paper is deemed significant enough to merit mention. Furthermore, as an expert in the field of tissue engineering materials, Hubbell's opinion would be entitled to significant weight, so the Examiner's assertion that "such a statement would be a matter of opinion" is irrelevant.

The Examiner further asserts that Hubbell does not indicate that the self-assembled peptides are ECM-like but rather that ECM-like material is desirable. Applicants submit that while Hubbell does not explicitly state that the self-assembled peptides are ECM-like, this is the clear implication from what he does in fact state. Hubbell refers to "the fibrillar structure of the natural ECM" and its importance in controlling cellular behavior (see p. 555, sentence bridging left and right-hand columns) and then goes on to state that "*in situ* fibril formation may only now be coming into reach (e.g., using the concepts of self-assembly)", at which point he references Applicants' work. Thus Hubbell does indeed indicate that the claimed invention has favorable ECM-like properties. While Hubbell also notes that technical hurdles remain, the fact that Hubbell may not have considered the instant invention to be a final solution to the problem of obtaining an ideal ECM-like material does not imply that he did not consider it "acceptable", as suggested by the Examiner. There is no need for an invention to be a "final" or perfect solution to a problem in order to render it a non-obvious and valuable contribution to the state of the art.

As pointed out previously, the Federal Circuit has recognized that, "Appreciation by contemporaries skilled in the field of the invention is a useful indicator of whether the invention would have been obvious to such persons at the time it was made." *Vulcan Engineering Co., Inc.*

v. Fata Aluminum, Inc., 278 F.3d 1366 (Fed. Cir. 2002), and "the secondary considerations are...essential components of the obviousness determination" *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998). Applicants respectfully request that the Examiner give the above-mentioned secondary considerations the weight they deserve in evaluating the patentability of the claimed invention.

Given that claim 1 is non-obvious, Applicants submit that claims 2, 3, 5-8, 19, 20, 22-24, and 27-32, which depend on claim 1, are also non-obvious.

With respect to claim 19, Applicants reiterate that the Examiner's suggestion that it would have been obvious to encapsulate chondrocytes to provide a source of the collagen is based entirely on hindsight.

The Examiner has also stated that compression as required by claim 30 would not result in a different membrane or matrix than that obtained by Holmes and that handling the membrane of Holmes would inherently result in some compression. Applicants respectfully disagree but have amended the claim to recite that the macroscopic scaffold is subjected to static or dynamic compression or a combination thereof according to a predetermined compression scheme. Incidental handling does not constitute a predetermined compression scheme. New claim 34 is recites features of a particular compression scheme. Support is found, e.g., at p. 8, lines 11-19.

Claim 4 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Holmes and Hubbell as applied to claims 1-3, 5-8, 19, and 21-32 and further in view of Holmes et al. (PNAS). Given that claim 1 is non-obvious, Applicants submit that claim 4, which depends on claim 4, is also non-obvious.

Claim 20 stands objected to as being dependent on a rejected claim, namely claim 1. Applicants submit that since claim 1 is non-obvious, claim 20 is allowable.

In summary, Applicants submit that it is only through the use of hindsight that the Examiner finds the claimed invention obvious in view of Holmes and Hubbell. Furthermore, the combination of Holmes and Hubbell fails to enable the invention because neither of them teaches or suggests the use of an osmotically active solute that does not induce peptide self-assembly, and any scaffold formed according to the methods taught or suggested by Holmes or Hubbell would differ materially from the presently claimed scaffolds. In addition, the Examiner has not

accorded appropriate weight to the above-mentioned secondary considerations, which argue strongly in favor of non-obviousness. Withdrawal of the rejection is respectfully requested.

New Claims

Based in part on discussion with the Examiner, a number of new claims are presented herein.

New claim 34 is directed to a macroscopic scaffold as in claim 1, wherein the macroscopic scaffold has a predetermined shape or volume. Support for this claim is found, e.g., at p. 3, lines 9-10. While Hubbell discloses scaffolds having a predetermined shape or volume, such a suggestion is found nowhere in Holmes and would not result from practicing the methods described by him or by Hubbell, or modifications thereof that would be obvious from the combination thereof.

New claim 35 is directed to a macroscopic scaffold as in claim 1, wherein the cells encapsulated in said macroscopic scaffold are substantially uniformly distributed therein. Support for this claim is found, e.g., at p. 6, lines 16-17. Neither Holmes nor Hubbell teaches or suggests such a macroscopic scaffold wherein cells encapsulated in the macroscopic scaffold are substantially uniformly distributed therein. Furthermore, there is no evidence to suggest that practicing the methods described by Holmes or by Hubbell, or modifications thereof that would be obvious from the combination thereof, would result in such a macroscopic scaffold.

New claims 36-39 are product by process claims that set forth a variety of methods for preparing the macroscopic scaffold of claim 1. Support for these claims is found, e.g., at p. 15, lines 1-5. Claim 36 is additionally supported by original claim 9 and at p. 2, lines 13-15 and 18-21 of the specification. Claim 37 is additionally supported by original claim 9 and at p. 23, lines 24-25. Claims 38 and 39 are additionally supported by original claim 10 and at p. 23, line 24 – p. 24, line 6.

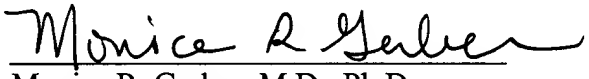
New claim 40 is drawn to a macroscopic scaffold as in claim 1, wherein said macroscopic scaffold is subjected to static or dynamic compression, or a combination thereof, sufficient to increase secretion by cells encapsulated therein. Support for this claim is found, e.g., at p. 8, lines 23-24 and in original claim 15.

In conclusion, in view of the amendments and remarks presented herein, none of the cited art anticipates any of the claims pending in the instant application nor renders them obvious. Applicants therefore respectfully submit that the present case is in condition for allowance. A Notice to that effect is respectfully requested.

If, at any time, it appears that a phone discussion would be helpful, the undersigned would greatly appreciate the opportunity to discuss such issues at the Examiner's convenience. The undersigned can be contacted at (617) 248-5000 or (617) 248-5071 (direct dial).

Please charge any fees associated with this filing, including that for any necessary extensions of time, or apply any credits, to our Deposit Account No. 03-1721.

Respectfully submitted,



Monica R. Gerber, M.D., Ph.D.
Registration Number 46,724
Date: Feb. 17, 2005

Choate, Hall & Stewart
Exchange Place
53 State Street
Boston, MA 02109
(617) 248-5000
3828599_1.DOC

Exhibit A

PNAS Information for Authors

REVISED January 2005

PURPOSE AND SCOPE

The Proceedings of the National Academy of Sciences USA (PNAS) publishes research reports, commentaries, perspectives, and colloquium papers. In accordance with the guiding principles established by George Ellery Hale in 1914, PNAS publishes brief first announcements of Academy members' and foreign associates' (hereafter referred to as members) more important contributions to research and of work that appears to a member to be of particular importance. PNAS is a general science journal with a broad scientific audience. All papers should be intelligible to this audience.

Research Reports describe the results of original research of exceptional importance.

Commentaries call attention to papers of particular note and are written at the invitation of the Editorial Board.

Perspectives present a viewpoint on an important area of research and are written at the invitation of the Editorial Board.

Colloquium Papers are reports of scientific colloquia held under Academy auspices.

EDITORIAL POLICIES

Submission and Review

Manuscripts may be submitted to PNAS through any of the following three tracks:

Track I. An Academy member may "communicate" manuscripts for others that are within the member's area of expertise. Prior to submission to PNAS, the member obtains outside reviews of the paper from at least two qualified referees, each from a different institution and not from the authors' institutions. The names and contact information, including e-mails, of referees who reviewed the paper, along with the reviews and the authors' response, must be included. Reviews should be submitted on the PNAS review form.

Track II. Authors (members and nonmembers) may submit their manuscripts directly to the PNAS office. In a cover letter, authors may recommend appropriate Editorial Board members, NAS members who are expert in the paper's scientific area, and qualified referees. The Editorial Board may choose a member as editor for the paper who is not on that list or may reject the paper without further review. The member-editor conducts the review of the paper as described for Track I. A link to a List of NAS Members and their research interests is on the PNAS site map. Authors may also suggest qualified referees. The name of the member-editor, who may remain anonymous to the author until the paper is accepted, will be published in PNAS as editor of the article.

Track III. An Academy member may submit his or her own manuscripts for publication. Members' submissions must be accompanied by the name of knowledgeable colleague(s) who reviewed the paper, along with the review(s) and the authors' response.

All Tracks. Manuscripts submitted under any of the three tracks are evaluated by the Editorial Board. The Board may reject manuscripts without further review or may subject manuscripts to review and reject those that do not meet the standards of the journal. Manuscripts rejected by one member cannot be resubmitted through another member. When revisions are requested prior to final decision, revised papers must be received within three months or they will be treated as new submissions.

In the journal, Track I, II, and III papers are distinguished respectively as "Communicated by," "Edited by," and "Contributed by" the responsible member. Track II papers have an additional identifying footnote.

Journal Policies

(*i*) Articles are accepted provided they have not been **Published Previously** or concurrently submitted for publication elsewhere. Related manuscripts that are in press or submitted elsewhere must be included with your PNAS submission.

Figures or tables that have been published elsewhere must be identified, and permission of the copyright holder for *both* the print and the online editions of the journal must be provided (see sample permission request letter at www.pnas.org/misc/permissions_letter.rtf).

(*ii*) **Authorship** should be limited to those who have contributed substantially to the work. The corresponding author must have obtained permission from all authors for the submission of each version of the paper and for any change in authorship.

All collaborators share some degree of responsibility for any paper they coauthor. Some coauthors have responsibility for the entire paper as an accurate, verifiable report of the research. These include coauthors who are accountable for the integrity of the data reported in the paper, carry out the analysis, write the manuscript, present major findings at conferences, or provide scientific leadership to junior colleagues. Coauthors who make specific, limited contributions to a paper are responsible for their contributions but may have only limited responsibility for other results. While not all coauthors may be familiar with all aspects of the research presented in their paper, all collaborators should have in place an appropriate process for reviewing the accuracy of the reported results.

Authors are strongly encouraged to indicate their specific contributions to the published work. If provided, this information will be posted online as a footnote to the paper. Examples of designations include:

- Designed research
- Performed research
- Contributed new reagents or analytic tools
- Analyzed data
- Wrote the paper

An author may list more than one contribution, and more than one author may have contributed to the same aspect of the work.

(*iii*) All authors, members, referees, and editors must disclose any association that poses a **Conflict of Interest** in connection with the manuscript. Authors must acknowledge all funding sources supporting the work.

(*iv*) A completed form assigning **Copyright** to the National Academy of Sciences must be returned to the PNAS office before the paper can be published. This and other forms are available at www.pnas.org.

(*v*) The Academy may distribute **Embargoed** copies of an article to the press prior to publication.

(*vi*) Research involving **Human and Animal Subjects** must have been approved by the author's institutional review board. All

Exhibit B

About PNAS

Proceedings of the National Academy of Sciences of the United States of America

PNAS is one of the world's most-cited multidisciplinary scientific serials. Since its establishment in 1914, it continues to publish cutting-edge research reports, commentaries, reviews, perspectives, colloquium papers, and actions of the Academy. Coverage in PNAS spans the biological, physical, and social sciences. PNAS is published weekly in print, and daily online in PNAS Early Edition. The PNAS impact factor is 10.3 for 2003. PNAS is available by subscription.

PNAS is abstracted and/or indexed in: Index Medicus, PubMed Central, Current Contents, Medline, SPIN, JSTOR, ISI Web of Science, and BIOSIS.

PNAS Online

- Free Content
- Special Features
- Most recently read articles online
- Most recently cited articles online
- Developing countries with free access to PNAS Online

PNAS RSS Feeds XML

About Track II

Advertising

Press Information

Frequently Asked Questions

Rights and Permissions

PNAS Online

PNAS Online launched in January 1997 and now receives nearly 6 million hits per month. The site contains the full text, figures, tables, equations, and references of all articles in PNAS dating back to 1990.

PNAS articles are also published online before print in a feature called PNAS Early Edition as soon as they are accepted and final author changes are made. Release of articles became daily in June 2002. The date of online release is posted on the website and is the official date of publication. Papers are published online 1 to 5 weeks before they appear in print. PNAS can now